PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Chen, Fang		
Serial No.:	To be assigned	Case No.: 20084YCA	Art Unit: 1646
Filed:	On even date herewith		
For:	DNA MOLECULES ENCODING HUMAN NUCLEAR RECEPTOR PROTEIN nNR7-1 (As amended herein)		Examiner: Michael Pak

Assistant Commissioner of Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT,
37 C.F.R. §1.111, 1.115

EXPRESS MAILING CERTIFICATE, 37 C F R 1 10
DATE OF DEPOSIT March 4, 2002
EXPRESS MAILING NO EL523911383 US

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS EXPRESS MAIL "POST OFFICE TO ADDRESSEE" ON THE ABOVE DATE IN AN ENVELOPE ADDRESSED TO :

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MAILED BY Christine Cuffe
DATE 3-4-02

Sir:

Preliminary to the examination of this Rule 53(b) continuation application, please calculate the filing fee due based on cancellation of claims 1-19 and 35-38, and entry of amended claims 20-34. Please enter these amendments and consider the following remarks in response to the outstanding Office Action in currently co-pending U.S. Application Serial No. 09/209,069, filed December 10, 1998. A Notice of Appeal was filed in the '069 application on October 5, 2001. A Petition to Extend Time under 37 C.F.R. §1.136(a) for three (3) months is entered on an even date herewith in the '069 file to continue pendency of the this application, up to and including at least Tuesday, March 5, 2002. Applicants intend to cease further prosecution of the '069 case in favor of this above-identified continuation application. Please charge the three month extension fee, as a large entity, to Deposit Account No. 13-2755. In the event any additional extension of time is required, please treat this paper as a request under 37 C.F.R. §1.136(a) to extend the time as required, and charge Deposit Account No. 13-2755 the appropriate fee as a large entity. Please credit any overpayment or charge any fee deficiency to Deposit Account No. 13-2755.

IN THE TITLE:

At page 1, line 6, please delete the current title and insert the following title:
-- DNA MOLECULES ENCODING HUMAN NUCLEAR RECEPTOR PROTEIN nNR7-1 --.

IN THE SPECIFICATION:

At page 1, lines 1-3, please delete the following:

"Express Mail No. EM230308657US
December 10, 1998
Application of: Fang Chen".

At page 1, lines 11-13, please delete the continuing data and insert the following explanation for the continuing data related to the above-identified application:
-- This application is a continuation of U.S. Application Serial Number 09/209,069, filed December 10, 1998, which claims the benefit, under 35 U.S.C. 119(e), of U.S. Provisional Application Serial Number 60/104,251, filed October 14, 1998, and U.S. Provisional Application Serial Number 60/069,401, filed December 12, 1997. --.

At page 1, lines 16-17, please delete the following:
"STATEMENT REGARDING FEDERALLY-SPONSORED R&D
Not applicable."

At page 1, lines 20-21, please delete the following:
"REFERENCE TO MICROFICHE APPENDIX
Not applicable."

IN THE CLAIMS:

Please cancel claims 1-19 and 35-38, without prejudice.

Please amend claims 20, 24 and 28 as follows:

20(Amended). A purified DNA molecule encoding a human nNR7-1 protein wherein said protein comprises the amino acid sequences as set forth in SEQ ID NO: 18.

24(Amended). A purified DNA molecule encoding a human nNR7-1 protein wherein said protein consists of the amino acid sequence as set forth in SEQ ID NO: 18.

28(Amended). A purified DNA molecule encoding a human nNR7-1 protein wherein said DNA molecule consists of the nucleotide sequence as set forth in SEQ ID NO: 17.

Please add new claims 39-42.

39(New). A purified DNA molecule encoding a human nNR7-1 protein wherein said DNA molecule comprises the nucleotide sequence as set forth in SEQ ID NO: 17.

40(New). An expression vector for expressing a human nNR7-1 protein in a recombinant host cell wherein said expression vector comprises a DNA molecule of claim 39.

41(New). A host cell which expresses a recombinant human nNR7-1 protein wherein said host cell contains the expression vector of claim 40.

42(New). A process for expressing a human nNR7-1 protein in a recombinant host cell, comprising:

(a) transfecting the expression vector of claim 40 into a suitable host cell; and,

(b) culturing the host cells of step (a) under conditions which allow expression of said the human nNR7-1 protein from said expression vector.

REMARKS

Claims 1-19 and 35-38 are cancelled above, without prejudice.

Claims 20-34 and 39-42 are pending in the above-identified Rule 53(b) continuation application. Applicants respectfully amend claims 20, 24 and 28 to so as to mimic pending claims in co-pending U.S Application Serial No. 09/209,069. Applicants respectfully reserve the right to pursue the non-elected subject matter of claims 1-19 and 35-38 in one or more future continuing applications.

A marked-up version of amended claims 20, 24 and 28 is attached hereto.

New claims 39-42 are added to more particularly point out and distinctly claim the present invention.

The title of the invention has been amended to more clearly recite the DNA molecules (and associated vectors, hosts and methods) recited in claims 20-34 and 39-42.

The continuing data has been amended to more correctly refer to the previously filed § 111 application (09/209,069) and provisional applications as claiming the benefit of priority filing under 35 U.S.C. 119(e).

First page material, now superfluous, has been deleted.

Claims 20, 24 and 28 are amended to specifically recite SEQ ID NOs. In addition, claim 20 is amended to recite nNR7-1, not nNR7.

No new matter is added by amendment to claims 20, 24 and 28 or entry of new claims 39-42.

Rejection of Claims 20-34 Under 35 U.S.C. § 103(a)

Claims 20-34 stand rejected in the '069 application under 35 U.S.C. § 103(a) as allegedly "being unpatenable over Lehmann et al. (J. Clin. Invest., 1998)", herein "Lehmann." Applicants respectfully disagree. Simply put, Lehman neither provides motivation nor instills in the artisan of ordinary skill in the art a reasonable expectation of isolating and characterizing the DNA molecules recited in pending claims 20-34. In review, Lehmann discloses a clone which is a truncated version of nNR7-1. *Lehmann does not disclose a full length clone (i.e., a DNA molecule encoding nNR7-1).* As noted previously, Lehmann vigorously takes the position, within the confines of an extremely reputable, peer-reviewed journal publication, that the hPXR clone represents the 'wild-type' version of this gene. As stated in Lehmann:

> Examination of the hPXR sequence revealed an in-frame CUG codon (nucleotides 304-306) surrounded by a favorable Kozak sequence (10). *There is precedent for the use of CUG codons to initiate translation of eukaryotic protein, including the nuclear receptor RARβ4 (10, 11).*[1] Initiation of translation at this CUG codon would yield a protein of 434 amino acids, three longer than mPXR1, with a predicted MW of 50kD.[2]

Lehmann then proceeds to discuss within the same paragraph experiments which, in his mind, show beyond a doubt that:

> "our results indicate that the CUG codon represents the principal translation initiation site for hPXR containing a functional DBD."[3]

Lehmann is so comfortable with what *Applicant has shown to be a truncated version* of the gene/expressed protein, that he proceeds to describe various assays which were conducted utilizing this truncated protein. To this end, Applicants respectfully take the position that Lehmann offers no motivation to attempt to isolate any additional DNA molecule other than the one that encodes hPXR, and therefore, does not instill any reasonable expectation that any such full-length clone could be identified. Why? Because it is evident that Lehmann (and

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[1] Citing Kozak et al., 1991, J. Biol. Chem. 266:19867-19870 (10) and Nagpal, et al., 1992, PNAS 89:2718-2722 (11), respectively.
[2] Lehmann at p. 1017, column 2, last paragraph - p. 1018, column 1, line 1. (emphasis added).
[3] id. at p.1018, colum2, lines 1-3.

presumably the reviewers of this *JBC* article) are satisfied that the hPXR sequence represented the correct form of protein. If so, then there is no need (i.e., motivation) to experiment further for any additional forms. Again, even if the artisan of ordinary skill chose such a course, Lehmann would not render any such clone (such as NR7-1) obvious in view of its explicit and straightforward teaching regarding hPXR. Therefore, Applicant respectfully takes the position that it is nothing more than hindsight analysis on the part of the Examiner to suggest that Applicant's isolation and characterization of a full length clone (*an open reading frame complete with an initiating ATG and encoding some 39 additional amino acids at the NH_2-terminal end*) would be obvious in view of Lehmann. In stark contrast, the bottom line in Lehmann is that the issue is decided: hPXR is the sequence of interest, with no additional cloning experiments being necessary or warranted.

Therefore, Applicant has provided a full-length, wild-type version of the cDNA encoding this nuclear receptor (as opposed to an NH_2-terminal truncated version) which is in no way contemplated by Lehmann. Such a clone allows the skilled artisan may be more confident in selecting compounds involved in the modulation of CYP3A4. To this end, Applicant respectfully requests that the §103(a) rejection put forth in the '069 application not be applied in the above-identified continuation application. Applicant respectfully reiterate their earlier claims 20-34, as well as new claims 39-42, are in proper form for allowance. Early action to that end is earnestly solicited. The Examiner is invited to contact the undersigned attorney if clarification is required on any aspect of this response, or if any of the claims are considered to require further amendment to be placed in condition for allowance after entry of this Amendment.

Respectfully submitted,

Date: March 4, 2002

By _____
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MARKED-UP VERSION OF APPLICATION AS AMENDED HEREIN

20(Amended). A purified DNA molecule encoding a human nNR7-1 protein wherein said protein comprises the amino acid sequence [as follows:

MTVTRTHHFK EGSLRAPAIP LHSAAAELAS NHPRGPEANL EVRPKESWNH
ADFVHCEDTE SVPGKPSVNA DEEVGGPQIC RVCGDKATGY HFNVMTCEGC
KGFFRRAMKR NARLRCPFRK GACEITRKTR RQCQACRLRK CLESGMKKEM
IMSDEAVEER RALIKRKKSE RTGTQPLGVQ GLTEEQRMMI RELMDAQMKT
FDTTFSHFKN FRLPGVLSSG CELPESLQAP SREEAAKWSQ VRKDLCSLKV
SLQLRGEDGS VWNYKPPADS GGKEIFSLLP HMADMSTYMF KGIISFAKVI
SYFRDLPIED QISLLKGAAF ELCQLRFNTV FNAETGTWEC GRLSYCLEDT
AGGFQQLLLE PMLKFHYMLK KLQLHEEEYV LMQAISLFSP DRPGVLQHRV
VDQLQEQFAI TLKSYIECNR PQPAHRFLFL KIMAMLTELR SINAQHTQRL
LRIQDIHPFA TPLMQELFGI TGS,] as set forth in [the three-letter abbreviation in] SEQ ID NO: 18.

24(Amended). A purified DNA molecule encoding a human nNR7-1 protein wherein said protein consists of the amino acid sequence [as follows:

MTVTRTHHFK EGSLRAPAIP LHSAAAELAS NHPRGPEANL EVRPKESWNH
ADFVHCEDTE SVPGKPSVNA DEEVGGPQIC RVCGDKATGY HFNVMTCEGC
KGFFRRAMKR NARLRCPFRK GACEITRKTR RQCQACRLRK CLESGMKKEM
IMSDEAVEER RALIKRKKSE RTGTQPLGVQ GLTEEQRMMI RELMDAQMKT
FDTTFSHFKN FRLPGVLSSG CELPESLQAP SREEAAKWSQ VRKDLCSLKV
SLQLRGEDGS VWNYKPPADS GGKEIFSLLP HMADMSTYMF KGIISFAKVI
SYFRDLPIED QISLLKGAAF ELCQLRFNTV FNAETGTWEC GRLSYCLEDT
AGGFQQLLLE PMLKFHYMLK KLQLHEEEYV LMQAISLFSP DRPGVLQHRV
VDQLQEQFAI TLKSYIECNR PQPAHRFLFL KIMAMLTELR SINAQHTQRL
LRIQDIHPFA TPLMQELFGI TGS,] as set forth in [the three-letter abbreviation in] SEQ ID NO: 18.

28(Amended). A purified DNA molecule encoding a human nNR7-1 protein wherein said DNA molecule consists of the nucleotide sequence as set forth in SEQ ID NO: 17[, as follows:

TCCATCCTAA TACGACTCAC TATAGGGCTC GAGCGGCCGC CCGGGCAGGT
CTTTTGGCCT GCTGGGTTAG TGCTGGCAGC CCCCTGAGGC CAAGGACAGC
AGCATGACAG TCACCAGGAC TCACCACTTC AAGGAGGGGT CCCTCAGAGC
ACCTGCCATA CCCCTGCACA GTGCTGCGGC TGAGTTGGCT TCAAACCATC
CAAGAGGCCC AGAAGCAAAC CTGGAGGTGA GACCCAAAGA AAGCTGGAAC
CATGCTGACT TTGTACACTG TGAGGACACA GAGTCTGTTC CTGGAAAGCC
CAGTGTCAAC GCAGATGAGG AAGTCGGAGG TCCCCAAATC TGCCGTGTAT
GTGGGGACAA GGCCACTGGC TATCACTTCA ATGTCATGAC ATGTGAAGGA
TGCAAGGGCT TTTTCAGGAG GGCCATGAAA CGCAACGCCC GGCTGAGGTG
CCCCTTCCGG AAGGGCGCCT GCGAGATCAC CCGGAAGACC CGGCGACAGT
GCCAGGCCTG CCGCCTGCGC AAGTGCCTGG AGAGCGGCAT GAAGAAGGAG
ATGATCATGT CCGACGAGGC CGTGGAGGAG AGGCGGGCCT TGATCAAGCG
GAAGAAAAGT GAACGGACAG GGACTCAGCC ACTGGGAGTG CAGGGGCTGA
CAGAGGAGCA GCGGATGATG ATCAGGGAGC TGATGGACGC TCAGATGAAA
ACCTTTGACA CTACCTTCTC CCATTTCAAG AATTTCCGGC TGCCAGGGGT
GCTTAGCAGT GGCTGCGAGT TGCCAGAGTC TCTGCAGGCC CCATCGAGGG
AAGAAGCTGC CAAGTGGAGC CAGGTCCGGA AAGATCTGTG CTCTTTGAAG
GTCTCTCTGC AGCTGCGGGG GGAGGATGGC AGTGTCTGGA ACTACAAACC
CCCAGCCGAC AGTGGCGGGA AAGAGATCTT CTCCCTGCTG CCCCACATGG
CTGACATGTC AACCTACATG TTCAAAGGCA TCATCAGCTT TGCCAAAGTC
ATCTCCTACT TCAGGGACTT GCCCATCGAG GACCAGATCT CCCTGCTGAA
GGGGGCCGCT TTCGAGCTGT GTCAACTGAG ATTCAACACA GTGTTCAACG
CGGAGACTGG AACCTGGGAG TGTGGCCGGC TGTCCTACTG CTTGGAAGAC
ACTGCAGGTG GCTTCCAGCA ACTTCTACTG GAGCCCATGC TGAAATTCCA
CTACATGCTG AAGAAGCTGC AGCTGCATGA GGAGGAGTAT GTGCTGATGC
AGGCCATCTC CCTCTTCTCC CCAGACCGCC CAGGTGTGCT GCAGCACCGC
GTGGTGGACC AGCTGCAGGA GCAATTCGCC ATTACTCTGA AGTCCTACAT
TGAATGCAAT CGGCCCCAGC CTGCTCATAG GTTCTTGTTC CTGAAGATCA
TGGCTATGCT CACCGAGCTC CGCAGCATCA ATGCTCAGCA CACCCAGCGG
CTGCTGCGCA TCCAGGACAT ACACCCCTTT GCTACGCCCC TCATGCAGGA
GTTGTTCGGC ATCACAGGTA GCTGAGCGGC TGCCCTTGGG TGACACCTCC

GAGAGGCAGC CAGACCCAGA GCCCTCTGAG CCGCCACTCC CGGGCCAAGA
CAGATGGACA CTGCCAAGAG CCGACAATGC CCTGCTGGCC TGTCTCCCTA
GGGAATTCCT GCTATGACAG CTGGCTAGCA TTCCTCAGGA AGGACATGGG
TGCCCCCCAC CCCCAGTTCA GTCTGTAGGG AGTGAAGCCA CAGATTCTTA
CGTGGAGAGT GCACTGACCT GTAGGTCAGG ACCATCAGAG AGGCAAGGTT
GCCCTTTCCT TTTAAAAGGC CCTGTGGTCT GGGGAGAAAT CCCTCAGATC
CCACTAAAGT GTCAAGGTGT GGAAGGGACC AAGCGACCAA GGATAGGCCA
TCTGGGGTCT ATGCCCACAT ACCCACGTTT GTTCGCTTCC TGAGTCTTTT
CATTGCTACC TCTAATAGTC CTGTCTCCCA CTTCCCACTC GTTCCCCTCC
TCTTCCGAGC TGCTTTGTGG GCTCCAGGCC TGTACTCATC GGCAGGTGCA
TGAGTATCTG TGGGAGTCCT CTAGAGAGAT GAGAAGCCAG GAGGCCTGCA
CCAAATGTCA GAAGCTTGGC ATGACCTCAT TCCGGCCACA TCATTCTGTG
TCTCTGCATC CATTTGAACA CATTATTAAG CACCGATAAT AGGTAGCCTG
CTGTGGGGTA TACAGCATTG ACTCAGATAT AGATCCTGAG CTCACAGAGT
TTATAGTTAA AAAAACAAAC AGAAACACAA ACAATTTGGA TCAAAAGGAG
AAATGATAAG TGACAAAAGC AGCACAAGGA ATTTCCCTGT GTGGATGCTG
AGCTGTGATG GCGGGCACTG GGTACCCAAG TGAAGGTTCC CGAGGACATG
AGTCTGTAGG AGCAAGGGCA CAAACTGCAG CTGTGAGTGC GTGTGTGTGA
TTTGGTGTAG GTAGGTCTGT TTGCCACTTG ATGGGGCCTG GGTTTGTTCC
TGGGGCTGGA ATGCTGGGTA TGCTCTGTGA CAAGGCTACG CTGACAATCA
GTTAAACACA CCGGAGAAGA ACCATTTACA TGCACCTTAT ATTTCTGTGT
ACACATCTAT TCTCAAAGCT AAAGGGTATG AAAGTGCCTG CCTTGTTTAT
AGCCACTTGT GAGTAAAAAT TTTTTTGCAT TTTCACAAAT TATACTTTAT
ATAAGGCATT CCACACCTAA GAACTAGTTT TGGGAAATGT AGCCCTGGGT
TTAATGTCAA ATCAAGGCAA AAGGAATTAA ATAATGTACT TTTGGCTAGA
GGGGTAAACT TTTTTGGCCT TTTTCTGGGG AAAATAATGT GGGGGTGTGG
(SEQ ID NO: 17)].